The Complementary Roles of Photoscreening and Clinical Referrals for Amblyopia Risk Factor Detection

Os Papéis Complementares da Fotorrefração e da Referenciação Clínica na Deteção de Fatores de Risco para a Ambliopia

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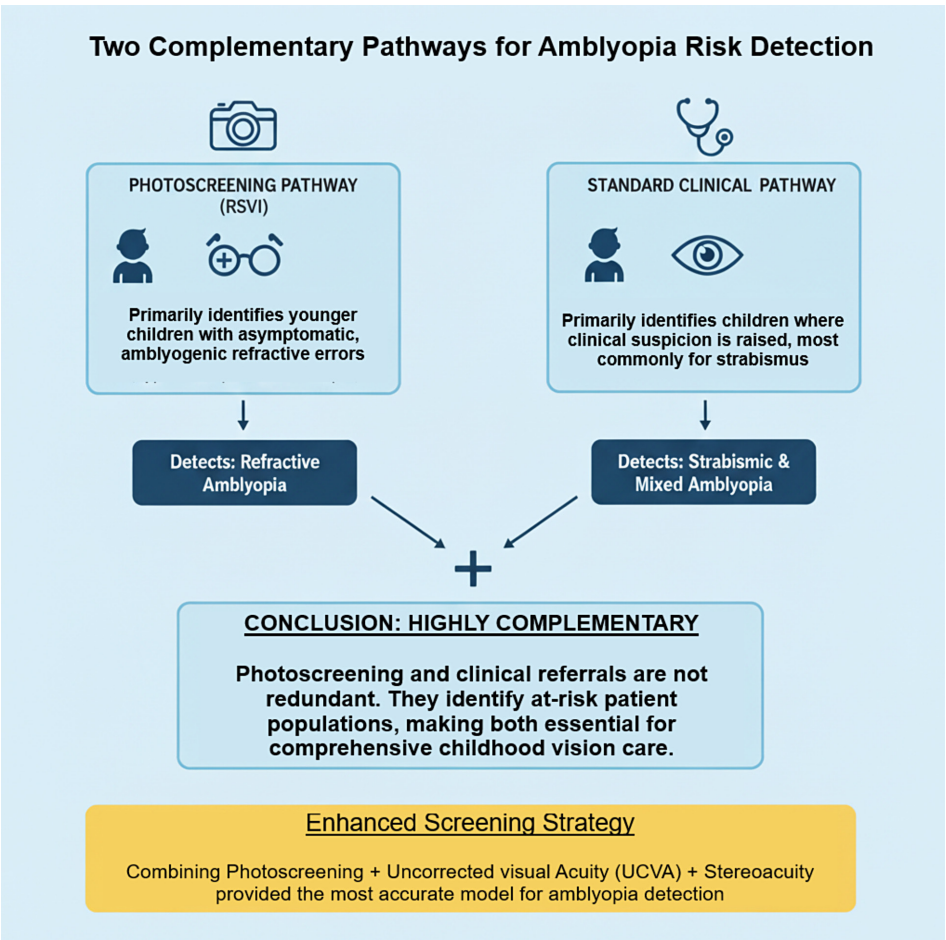

GRAPHICAL ABSTRACT

ABSTRACT

INTRODUCTION: Many major health organizations recommend vision screening at least once between 3 and 5 years of age. In Portugal, in addition to clinical screening, the "Rastreio de Saúde Visual Infantil" (RSVI) program provides photoscreening at ages 2 and 4.

We aimed to compare the demographic and clinical characteristics of children (aged 2-5 years) referred to a tertiary ophthalmology service by the RSVI screening program versus standard clinical referrals, and to evaluate the diagnostic performance of different models for detecting amblyopia and its risk factors.

METHODS: This observational, cross-sectional study analyzed records of 541 children, categorized into a Screening Referral Group (SRG, n=338), referred by RSVI, and a Standard Referral Group (STG, n=203), referred by pediatricians or family medicine physicians. Demographic, clinical, and refractive data were compared. The performance of screening models combining photoscreening (RSVI and AAPOS 2021 criteria), uncorrected visual acuity (UCVA), and stereopsis assessment was assessed using ROC analysis.

RESULTS: The SRG was younger (p<0.001) and had a higher prevalence of hypermetropic refractive errors (85.5% *vs* 54.2%), greater spherical equivalent, and greater anisometropia (p<0.001). Conversely, the STG had a higher prevalence of strabismus (19.2% *vs* 1.8%, p<0.001). The overall rate of amblyopia was similar (6.5% *vs* 6.7%), but it was primarily refractive in the SRG and strabismic/mixed in the STG. A model combining AAPOS photoscreening criteria with UCVA and stereoacuity had the highest diagnostic accuracy for amblyopia (AUC 0.932). A model combining RSVI criteria, UCVA, and stereoacuity was superior to RSVI alone for detecting amblyopia, strabismus, or the need for glasses (AUC 0.913 *vs* 0.760).

CONCLUSION: Photoscreening and standard clinical referrals are highly complementary pathways that identify significantly different patient populations. Photoscreening is effective at detecting presymptomatic amblyogenic refractive errors in younger children, while clinical suspicion remains crucial for identifying strabismus. Multi-modal screening strategies may lead to a more effective screening program.

KEYWORDS: Amblyopia/diagnosis; Child; Refraction, Ocular; Refractive Errors; Risk Factors; Vision Screening.

RESUMO

INTRODUÇÃO: As principais organizações de saúde recomendam o rastreio visual pelo menos uma vez entre os 3 e os 5 anos de idade. Em Portugal, para além do rastreio clínico, o programa Rastreio de Saúde Visual Infantil (RSVI) realiza um fotorrastreio aos 2 e 4 anos.

O objetivo do estudo foi comparar as características demográficas e clínicas de crianças (2-5 anos) referenciadas para um serviço de oftalmologia terciário através do programa de rastreio RSVI versus referenciação clínica padrão, e avaliar o desempenho diagnóstico de diferentes modelos para a deteção de ambliopia e dos seus fatores de risco.

MÉTODOS: Estudo observacional e transversal com 541 crianças divididas em dois grupos: Grupo de Referenciação por Rastreio (SRG, n=338), referenciado pelo RSVI; e Grupo de Referenciação Padrão (STG, n=203), referenciado por pediatras ou médicos de família. Foram comparados dados demográficos, clínicos e refrativos. A performance de modelos de rastreio que combinam fotorrastreio (critérios RSVI e AAPOS 2021), acuidade visual não corrigida (AVNC) e estereopsia foi avaliada com análise ROC.

RESULTADOS: O grupo SRG era mais novo (p<0,001) e apresentou maior prevalência de erros refrativos hipermetrópicos (85,5% *vs* 54,2%), maior equivalente esférico e maior anisometropia (p<0,001). O grupo STG apresentou uma prevalência superior de estrabismo (19,2% *vs* 1,8%, p<0,001). A taxa global de ambliopia foi semelhante (6,5% *vs* 6,7%), sendo predominantemente refrativa no SRG e estrábica/mista no STG. Um modelo que combina os critérios de fotorrastreio da AAPOS com AVNC e estereopsia demonstrou a maior precisão diagnóstica para ambliopia (AUC 0,932). A

combinação dos critérios RSVI com AVNC e estereopsia foi superior ao RSVI isoladamente para a deteção de ambliopia, estrabismo ou necessidade de óculos (AUC 0,913 *vs* 0,760).

CONCLUSÃO: O fotorrastreio e a referenciação clínica são vias complementares que identificam populações de doentes distintas. O fotorrastreio é eficaz a detetar erros refrativos ambliogénicos em crianças mais novas, enquanto a suspeita clínica é crucial para identificar estrabismo. Estratégias de rastreio multimodais podem melhorar a eficácia do programa.

PALAVRAS-CHAVE: Ambliopia/diagnóstico; Criança; Erros Refrativos; Fatores de Risco; Rastreio da Visão; Refração Ocular.

INTRODUCTION

Amblyopia is a leading cause of monocular visual impairment in childhood, typically arising from abnormal visual experience during critical periods and most often associated with strabismus and/or anisometropia.[1] Recent meta-analyses estimate a global prevalence of around 1.3%–1.5%, underscoring its public health relevance and the potential lifetime impact of untreated cases.[1,2] Early identification and treatment can substantially improve visual outcomes, supporting the rationale for organized detection strategies.[3]

Several major Health Organizations recommend vision screenings during the preschool years.[4-6] The U.S. Preventive Services Task Force (USPSTF) recommends screening at least once between ages 3–5 years to detect amblyopia or its risk factors, while evidence remains insufficient to determine the balance of benefits and harms under 3 years of age.[5] Professional guidelines further emphasize the role of instrument-based screening (photoscreening/autorefraction) to efficiently detect amblyopia risk factors in young children who cannot reliably perform optotype-based visual acuity testing.[3] The 2021 AAPOS uniform validation guidelines updated target failure levels and promoted age-adjusted thresholds; subsequent studies defined device-specific instrument referral criteria (IRC) for photoscreeners, highlighting trade-offs between sensitivity and specificity by age band.[6,7]

Across Europe, screening programs vary widely in age, setting, personnel, tests, and referral criteria,[8] which hampers comparison and optimization. Work from the EUSCREEN consortium shows both the feasibility of cost-effectiveness modeling as well as the current paucity of standardized data (e.g., sensitivity, specificity, attendance, loss-to-follow-up) needed to benchmark programs, while microsimulation suggests that cost-effectiveness depends strongly on local parameters (test performance, coverage, utilities).[9,10] In Portugal, the national "Rastreio de Saúde Visual Infantil" (RSVI) is a program delivered through primary care at ages 2 and 4 years, using photoscreening to identify potentially amblyogenic risk factors. Positive cases are referred for a complete ophthalmological exam in a hospital setting.[11]

While several studies[12,13] have evaluated the accuracy of photoscreeners against a gold-standard comprehensive eye examination, a knowledge gap remains regarding the clinical characteristics of children referred to tertiary care from these programs compared to those referred through traditional pathways of clinical suspicion. It is unclear whether these two referral streams identify similar patient populations, making one potentially redundant, or if they are complementary, each capturing a distinct subset of at-risk children. This has considerable implications for both the screening program efficiency and the role of the family medicine physicians and pediatricians.

This study aims to address these gaps by comparing demographic and clinical profiles of 2–5 year-olds referred via RSVI *versus* standard clinical pathways in a Portuguese tertiary center, and by evaluating the diagnostic performance of multi-modal screening models for outcomes of public health interest (amblyopia, strabismus, and need for spectacles).

MATERIAL AND METHODS

STUDY DESIGN AND POPULATION

An observational, cross-sectional study was conducted by retrospectively analyzing the ophthalmological electronic health records of all patients, aged 24 to 71 months (inclusive), who were referred to the ophthalmology department at our tertiary care institution. Only those referred for their first consultation between January 1st, 2024, and December 31, 2024 were included. Except in cases where a close second consultation (within 3 months) was done to assess cycloplegic refraction, only data from the first consultation were extracted.

The study population was divided into two groups based on the referral pathway. A Screening Referral Group (SRG) included all children referred by a positive Plusoptix® photoscreening examination done in a primary care setting ("Rastreio de Saúde Visual Infantil", RSVI). The Standard Referral Group (STG) included all children referred by a family medicine physician (FMP) or pediatrician. The study was conducted in accordance with the tenets of the Declaration of Helsinki, and approval was obtained from our Institutional Review Board (Centro Académico Clínico ICBAS-Santo António - 2024.055(050-DEFI/050-CE)).

CLINICAL EXAMINATION AND DATA COLLECTION

All children had undergone a comprehensive ophthalmic examination by an ophthalmologist. Collected data

included age (by year), sex, referral source and motive, uncorrected and best-corrected visual acuity (UCVA, BCVA) using age-appropriate optotypes, evaluation of ocular alignment and motility, stereoacuity testing (St) (Lang I test , considered positive when all three images were seen), Plusoptix®A09-obtained non-cycloplegic refractive error (non-cycloplegic streak retinoscopy only in those with unreadable or "hyper"/"myo" plusoptix® results), cycloplegic refractive error, and diagnosis at the first consultation. Cycloplegic refraction was performed via streak retinoscopy at least 30 minutes after administering two to three drops of 1% cyclopentolate, or in a second close consultation after 3 to 5 days of twice daily dose of 1% atropine drops. The historical screening results of RSVI at ages two and four were also extracted.

OPERATIONAL DEFINITIONS

Refractive errors were classified based on the cycloplegic refractive error measured. Hypermetropia was defined as a spherical equivalent ≥ +0.50 D and a cylinder ≤ ±0.75 D. Myopia was defined as a spherical equivalent of ≤ –0.50 D and a cylinder ≤ ±0.75 D. Astigmatism was defined as a cylindrical error > ±0.75 D, and further subclassified based on the spherical component into simple, compound, or mixed astigmatism.

A diagnosis of amblyopia required the presence of amblyogenic risk factors plus a BCVA inter-ocular difference of two or more logMAR lines or an age-adjusted BCVA in both eyes higher than 0.40 logMAR (<4 years), 0.30 logMAR (4 to <5 years) or 0.18 logMAR (≥5 years).[14]

Given that the clinical decision to prescribe glasses was at the discretion of the attending ophthalmologist, a secondary analysis was done to assess this outcome against a standardized objective threshold. For this sensitivity analysis, the need for refractive correction was defined according to the 2021 American Association for Pediatric Ophthalmology and Strabismus (AAPOS) guidelines applied to the patient's cycloplegic refraction measurements.[14]

Plusoptix® (PLX) screening criteria used for modelling included the RSVI criteria[11] and the AAPOS 2021 criteria, adapted by Arnold *et al*[6,7] (Table 1).

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS version 27 (IBM Corp., Armonk, NY). Descriptive statistics were calculated, with frequencies and percentages for categorical variables and medians with interquartile ranges (IQR) for non-normally distributed continuous variables.

For the comparative analysis between the SRG and STG, the Mann-Whitney U test was used for non-normally distributed continuous variables (age, refractive values), and Pearson's Chi-square test (or Fisher's exact test where appropriate) was used for categorical variables. Both absolute differences in proportions and relative risks with 95% confidence intervals (CI) were calculated for key binary outcomes. All comparisons of baseline characteristics and clinical outcomes were also stratified by age (2, 3, 4, and 5 years).

A significant portion of the sample had indeterminate outcomes for amblyopia (n=221, 40.9%) and stereoacuity (n=139, 25.7%), primarily due to age-related non-cooperation. As this missingness is likely not at random (MNAR), and is dependent on the unobserved cooperation level, listwise exclusion was used for the primary regression and ROC analyses, and this potential source of bias is addressed in the discussion.

Binary logistic regression models were developed to identify predictors of amblyopia, strabismus, and the need for refractive correction. Given the low number of events for the amblyopia outcome (n=21), we prioritized univariable analyses and a parsimonious multivariable model, to minimize the risk of overfitting.

The diagnostic performance of each screening model was evaluated by calculating sensitivity, specificity, and the Area Under the Curve (AUC) from Receiver Operating Characteristic (ROC) analysis. 95% CIs for AUCs were calculated. A *p*-value of <0.05 was considered statistically significant for all tests.

RESULTS

During the selected time period, 3410 children were photoscreened at 2 and 4 years of age (RSVI), 377 (11.1%) had positive criteria and were referred to our department, and 39 (10.3%)

Table 1. RSVI[11] and AAPOS 2021 (adapted by Arnold *et al*[6,7]) PLX referral criteria.

Referral Criteria	Category	Threshold (diopters)	How to measure
RSVI	Hypermetropia	≥ 2.0	Not specified
	Myopia	≤ -2.0	Not specified
	Astigmatism	≥ 2.0	
	Anisometropia	≥ 1.5	Not specified
Adapted AAPOS 2021	Hypermetropia	> 3.0D	SE hypermetropia
	Myopia	≤ -3.5 (< 4 years of age) ≤ -2.5 (≥ 4 years of age)	Meridional myopia*
	Astigmatism	≥ 3.5 (< 4 years of age) ≥ 2.5 (≥ 4 years of age)	
	Anisometropia	≥ 1.75	Meridional anisometropia**

* the most myopic end of the spherocylinder vector

** the difference (between both eyes) in the most myopic meridian of the spherocylinder vector

missed their ophthalmology appointment (Fig. 1).

During the selected time period, a total of 2152 children (ages 0-18, included) were referred to our department for a first ophthalmology appointment (excluding RSVI referrals). Out of these, 236 (11.0%) were between 2-5 years of age, and 33 (14.0%) missed their ophthalmology appointment (Fig. 1).

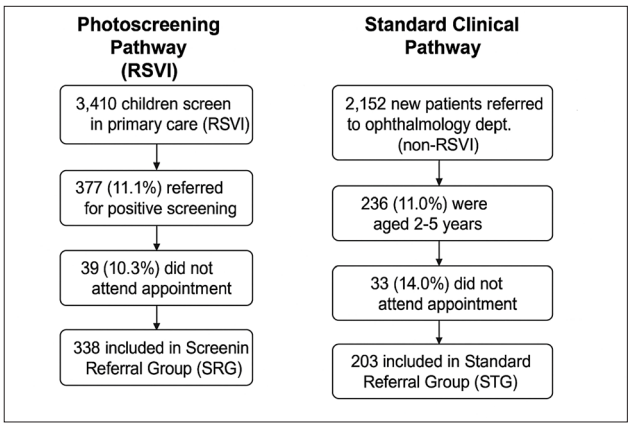

Figure 1. Patient flow chart.

BASELINE COHORT CHARACTERISTICS

A total of 541 children met the inclusion criteria. The mean age of the cohort was 3.24 (± 1.13) years, with a slight male predominance (295 males, 54.5%). The majority of children (n=338, 62.5%) were referred from the primary care screening program (SRG), while 203 (37.5%) were referred by FMP or pediatricians (STG). Across the entire sample, strabismus was present in 45 children (8.3%), and a definitive diagnosis of amblyopia was made in 21 children (3.9%). A significant portion of the sample, 221 children (40.9%), could not have their amblyopia status definitively determined due to lack of cooperation. An additional 30 children also did not cooperate for stereopsis testing. Spectacle correction was prescribed to 179 children (33.1%).

COMPARATIVE ANALYSIS: SCREENING (SRG) VERSUS STANDARD (STG) REFERRALS

Significant differences in demographic and clinical profiles were observed between the two referral groups, as detailed in Table 2.

Children referred from the screening program were significantly younger than those in the STG (p<0.001), as better illustrated in Fig. 2. The reasons for referral were markedly different between the two groups (p<0.001). The SRG was almost exclusively composed of referrals due to significant refractive errors and suspicion of impact on visual acuity (98.8%), whereas the STG was driven by clinical concerns such as suspected strabismus (28.6%), suspected low visual acuity (11.8%), or ophthalmological screening in the context of systemic diseases or family history (35.5%). This was reflected in the final diagnoses, with strabismus being over ten times more prevalent in the STG (19.2%) compared to the SRG group (1.8%) (p<0.001).

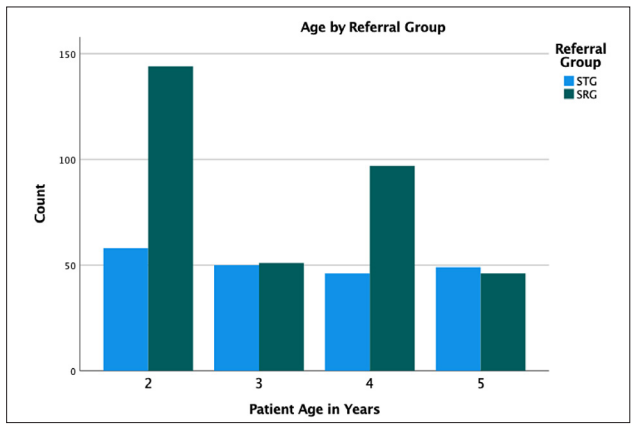

Figure 2. Age distribution by referral group.

The refractive profiles of the two groups were also distinct (p<0.001). The SRG was characterized by a high prevalence of hypermetropia and hypermetropic astigmatism (85.5%), while the STG had a substantially higher proportion of emmetropia (31.0%). Furthermore, the degree of SE anisometropia was significantly higher in the SRG (median 0.38 D) than in the STG (median 0.13 D) (p<0.001). Despite these differences in refractive error profiles, the overall observed rate of spectacle prescription was not significantly different between the two groups (34.0% in SRG *vs* 31.5% in STG, p=0.550). To test the robustness of this finding, a sensitivity analysis was performed by applying the standardized 2021 AAPOS criteria for significant refractive error to each patient's cycloplegic refraction measurements (Table 1 of the supplementary Annex 1). In this analysis, a significantly higher proportion of children in the SRG met the AAPOS criteria, compared to the STG (31.1% *vs* 17.7%, p<0.001). Whilst glasses prescription remains similar on the SRG even after applying the AAPOS criteria (34.0% *vs* 31.1%), it is much lower in STG (31.5% *vs* 17.7%, p<0.001), which means a significant proportion of prescriptions in this group were not because of potentially amblyogenic refractive errors.

When analyzing the prevalence of strabismus and glasses prescription by age and referral group, we find that strabismus is consistently much more prevalent in the STG versus SRG at all ages, and that glasses prescription is higher in SRG versus STG at 2 and 3 years of age, but lower at 4 and 5 years (Table 2 of the supplementary Annex 1).

Although amblyopia rates were similar between SRG and STG (6.5% *vs* 6.7%), the type of amblyopia was markedly different, with 100% (12/12) of amblyopias of the SRG being refractive amblyopias, and 66.7% (6/9) of amblyopias from STG being strabismic (3/9) or mixed (3/9) amblyopias (p=0.002, Fisher's exact test). The number of patients who did not cooperate for visual acuity and had an indeterminate amblyopia status (SRG 45.0% *vs* STG 34.0%) is also significant (p=0.015), and is likely related to the higher proportion of 2-year-old children in SRG. Age has a significant association with the ability to measure visual acuity (p<0.001), particularly in the 2-year age group, which comprised 66.4% of all cases that did not cooperate for visual acuity measurement. Table 3 better illustrates this data.

Table 2. Baseline Demographic and Clinical Characteristics of the Study Cohort, Stratified by Referral Source.

Characteristic	Screening Program Referrals (SRG) (N=338)	Standard Referrals (STG) (N=203)	Total Cohort (N=541)	*p*-value
Age, years [median (IQR)]	3.0 (2)	3.0 (2)	3.0 (2)	**<0.001***
Sex, n (%)				0.631
Female	151 (44.7%)	95 (46.8%)	246 (45.5%)	
Male	187 (55.3%)	108 (53.2%)	295 (54.5%)	
Referral Reason, n (%)				**<0.001**
Routine Screening	0 (0.0%) ASR -11.77	72 (35.5%) ASR 11.77	72 (13.3%)	
Suspected Strabismus	3 (0.9%) ASR -9.86	58 (28.6%) ASR 9.86	61 (11.3%)	
Suspected Low VA	334 (98.8%) ASR 20.72	24 (11.8%) ASR -20.72	358 (66.2%)	
Other	1 (0.3%) ASR -9.28	49 (24.1%) ASR 9.28	50 (9.2%)	
Strabismus, n (%)	6 (1.8%)	39 (19.2%)	45 (8.3%)	**<0.001**
Amblyopia, n (%)				0.925**
No	174 (93.5%)	125 (93.3%)	299 (93.4%)	
Yes	12 (6.5%)	9 (6.7%)	21 (6.6%)	
Glasses Prescribed, n (%)	115 (34.0%)	64 (31.5%)	179 (33.1%)	0.550
Refractive Error Category, n (%)				**<0.001**
Hyperopia/Hyperopic Astigmatism	289 (85.5%) ASR 8.41	110 (54.2%) ASR -8.41	399 (73.8%)	
Myopia/Myopic Astigmatism	10 (3.0%) ASR -2.23	18 (8.9%) ASR 2.23	28 (5.2%)	
Mixed Astigmatism	20 (5.9%) ASR 0.01	12 (5.9%) ASR -0.01	32 (5.9%)	
Emmetropia	19 (5.6%) ASR -9.34	63 (31.0%) ASR 9.34	82 (15.1%)	
Spherical Equivalent (D), median***	1.25 (1.38)	0.50 (1.25)		**<0.001**
SE Anisometropia (D), median***	0.38 (0.33)	0.13 (0.38)		**<0.001**

Statistical tests used were Mann-Whitney U Test for continuous variables and Pearson Chi-Square Test for categorical variables. Adjusted Stantardized Residuals (ASR) were calculated to understand which specific categories of Referral Reasons and Refractive Error Categories were driving the identified statistically significant difference between SRG and STG. * Although the median and IQR are identical between both groups, the distribution of 2- and 4-year-olds is significantly different (Mann-Whitney U Test), as better seen in Fig. 2. ** Cases impossible to determine were excluded from this analysis (221 / 40.9% of the whole sample, with a higher percentage on the SRG group (152 / 45.0%) than on the STG group (69 / 34.0%), likely due to the age differences between both groups. *** Calculated from non-cycloplegic Plusoptix® measurements.

Table 3. Visual acuity measurements cooperation by age.

Age (in years)	Visual acuity measurements cooperation		
	Yes (n / %)	No (n / %)	Total (n / %)
2	52 / 16.5% ASR -10.5	150 / 66.4% ASR 10.5	202 / 37.3%
3	55 / 17.5% ASR -0.6	46 / 20.4% ASR 0.6	101 / 18.7%
4	121 / 38.4% ASR 6.1	22 / 9.7% ASR -6.1	143 / 26.4%
5	87 / 27.6% ASR 5.4	8 / 3.5% ASR -5.4	95 / 17.6%
Total	315 / 100%	226 / 100%	541 / 100%

Pearson's Chi-square test reveals a *p*-value <0.001. Adjusted standardized residuals (ASR) were calculated, revealing that significantly more 2-year-olds did not cooperate than would be expected by chance, and significantly more 4 and 5-year-olds cooperated than would be expected by chance.

Given that a definitive diagnosis for amblyopia could not be established in 221 children (40.9% of the sample), primarily due to age-related non-cooperation, a sensitivity analysis was conducted to assess the impact of this missing data on the study's findings. The 221 indeterminate cases were distributed between the groups based on the observed proportions of non-cooperation (123 in SRG, 98 in STG). We tested two extreme scenarios: a "best-case" scenario, which assumed all indeterminate cases were not amblyopic, and a "worst-case" scenario, which assumed all indeterminate cases were amblyopic (Table 3 of the supplementary Annex 1).

LONGITUDINAL SCREENING SUB-ANALYSIS

Analysis of the historical photoscreening data (RSVI positive/negative at 2 and 4 years of age) provided insights into the real-world performance of the screening program. The results are summarized in Table 4.

Among children in the STG who had a documented

negative screening result at age two (RSVI): 16.8% were later diagnosed with strabismus, 18.7% had or developed refractive errors requiring spectacle correction, and 2.4% had or developed amblyopia. This highlights a group of children that potentially had amblyogenic risk factors that were not detected by the initial RSVI screening exam.

Among all children who passed their 2-year RSVI screening but failed at 4 years of age (SRG + STG), 25.7% were prescribed glasses, possibly revealing the development or progression of significant refractive errors in the intervening period. On the other hand, among children who were referred by the screening program at both ages two and four (SRG), but did not require treatment at the first referral, 60.9% also did not require treatment at the second referral, suggesting a potential for over-referral of this specific subset of stable, non-amblyogenic refractive errors.

PREDICTORS OF AMBLYOPIA POTENTIALLY MEASURABLE IN A PRIMARY CARE SETTING

Several uni and multivariate logistic regression analyses were performed on the 320 patients with a definitive amblyopia diagnosis (Yes/No), to identify independent predictors of the condition that could potentially be measured in a Primary Care Setting, with some modifications to the current RSVI program. Both the univariate logistic regression that included stereopsis and the multivariate regression included only the 290 patients that cooperated for both visual acuity and stereopsis testing.

Univariate logistic regressions showed that non-cycloplegic photoscreening refractive error criteria (RSVI) (OR 7.74) and UCVA of the worst eye (LogMar) (OR 56.74) achieved statistical significance with $p<0.001$, while stereopsis had a $p=0.006$ (OR 5.63). In a multivariate logistic regression that included these 3 variables (Hosmer and Lemeshow Test $p=0.061$), both uncorrected visual acuity (UCVA) of the worst eye and non-cycloplegic photoscreening (RSVI) were identified as strong, independent predictors of amblyopia. UCVA demonstrated the largest effect size (OR 12.15, $p=0.024$), while photoscreening showed the highest statistical certainty (OR 4.60, $p=0.018$). These results are presented in Table 5.

PERFORMANCE OF SCREENING MODELS

The diagnostic performance of various single- and multi-modal screening protocols was evaluated for different clinical outcomes, using the patient sample (n = 290) that had both a definitive amblyopia diagnosis as well as those that cooperated for stereopsis testing.

As shown in Table 6, the performance of models for detecting amblyopia varied substantially. Models incorporating UCVA showed superior performance. The Adapted AAPOS 2021 Plusoptix® criteria + UCVA + Stereopsis model achieved the highest AUC of 0.932, with a sensitivity of 100% and specificity of 83.5%. The RSVI criteria alone model had an AUC of 0.728, while the Adapted AAPOS model showed higher specificity (89.0%) but lower sensitivity (61.9%) (AUC 0.754).

For predicting the need for glasses, multi-modal approaches were again superior. The RSVI + UCVA + St model yielded the highest AUC of 0.931, with a sensitivity of 84.6% and specificity of 94.0%, closely followed by an UCVA + St model (AUC 0.925). RSVI criteria alone were far inferior (AUC 0.754) to the previous models, and the addition of PLX criteria to UCVA added very little to the models (UCVA alone had an AUC 0.867; UCVA + RSVI had an AUC 0.873).

The ability of the models to detect strabismus was mostly dependent on the inclusion of a non-refractive test component. Refractive-based screening performed poorly, with the RSVI criteria alone model having an AUC of 0.511,

Table 4. Analysis of Photoscreening History (RSVI at 2 and 4 years of age) for Key Clinical Outcomes.

Screening History	N	Clinical Outcome
Referred by STG + negative RSVI screening exam at 2 years of age	85	18 (16.8%) had strabismus
		20 (18.7%) required glasses
		2 (2.4%) had amblyopia
Negative RSVI screening exam at 2 years of age + positive RSVI screening exam at 4 years of age (SRG + STG)	105	27 (25.7%) required glasses
Positive RSVI screening exam at both 2 and 4 years of age (no treatment on the first referral) (SRG)	23	14 (60.9%) did not require glasses

A negative RSVI screening result at 2 years of age does not preclude a later diagnosis strabismus or refractive need.

Table 5. Multivariate Logistic Regression of Factors Associated with Amblyopia: RSVI Screening Plusoptix® Referral Criteria.

Predictor Variable	Odds Ratio (OR)	95% Confidence Interval	*p*-value
RSVI photoscreening criteria for referral (Positive *vs* Negative)	4.60	1.31 - 16.19	**0.018**
UCVA of the worst eye (per LogMar unit increase)	12.15	1.38 - 107.09	**0.024**
Stereopsis (Impaired *vs* Normal)	4.17	0.84 - 20.66	0.081

Analysis performed on N=290 patients with both a definitive amblyopia diagnosis (Yes/No) and collaboration for stereopsis testing.

Table 6. Diagnostic Performance of Selected Screening Models for Detection of Amblyopia.

Model	AUC	95% CI	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR-
AAPOS PLX + UCVA + St	0.932	0.901 - 0.964	100	83.5	28.6	100	6.06	0
UCVA + St	0.931	0.897 - 0.964	88.9	87.1	31.4	99.2	6.89	0.13
AAPOS PLX + UCVA	0.929	0.897 - 0.962	94.7	84.6	29.0	99.6	6.15	0.06
RSVI PLX + UCVA + St	0.913	0.861 - 0.964	88.9	84.6	27.6	99.1	5.77	0.13
RSVI PLX + UCVA	0.886	0.828 - 0.943	100	65.0	16.0	100	2.86	0
AAPOS PLX + St	0.818	0.704 - 0.931	75.0	87.6	30.0	98.0	6.05	0.29
RSVI PLX + St	0.770	0.678 - 0.862	90.0	63.5	14.9	98.9	2.47	0.16
AAPOS PLX	0.754	0.628 - 0.881	61.9	89.0	28.3	97.1	5.63	0.43
RSVI PLX	0.728	0.623 - 0.832	81.0	64.6	13.8	98.0	2.29	0.30

AAPOS PLX = Adapted AAPOS 2021 Plusoptix® criteria for referral[6,7]; RSVI PLX = RSVI Plusoptix® criteria for referral[11]; PPV = positive predictive value; NPV = negative predictive value; LR+ = positive likelihood ratio; LR- = negative likelihood ratio.

indicating performance no better than chance. In stark contrast, models incorporating stereoacuity were much more effective, with the AAPOS + St model achieving the highest AUC (0.862), with a 69.1% sensitivity and 100% specificity.

For the composite outcome of detecting any of the following: amblyopia, strabismus, or refractive error that needed refractive correction - a model combining the RSVI PLX criteria, UCVA, and stereoacuity (RSVI + UCVA + St) demonstrated the highest overall accuracy, with an AUC of 0.913, 79.1% sensitivity, and 95.2% specificity.

DISCUSSION

This study provides a comprehensive, real-world analysis of a primary care-based photoscreening program by comparing its referrals to those from standard clinical pathways, and evaluating the performance of various enhanced screening models.

The most striking findings are the clear distinctions between the SRG and STG populations. Both groups have a similar rate of amblyopia and glasses prescription, whilst having a different rate of strabismus and ammetropias. The screening program successfully identified a cohort of younger children, primarily with asymptomatic but significant anisometropic refractive errors — a known risk factor1 for refractive amblyopia. In contrast, the standard referral pathway was much more effective at identifying children with strabismus, and the sensitivity analysis for glasses prescription reveals that a large proportion of children receiving glasses in this group did not have potentially amblyogenic refractive errors. This demonstrates that the two pathways are not redundant. The RSVI screening program acts as an important tool for detecting potentially amblyogenic refractive errors that are unlikely to be noticed by parents or FMP / pediatricians, thereby allowing for intervention during the most sensitive period of visual development. Simultaneously, other means of ophthalmic screening and/or clinical suspicion remain crucial to correctly identify strabismus, among other ophthalmic diseases. These findings are relevant to better guide the FMP / Pediatricians on how to leverage the RSVI into their own screening practices.

The longitudinal sub-analysis provides critical insights into the real-world dynamics of the RSVI Screening Program. The identification of children who passed the screening at age two but were nonetheless diagnosed with strabismus or required refractive error corrections highlights the importance of FMP / Pediatricians in screening and detecting these cases, as well the potential for improvement of the RSVI Screening Program. Conversely, the small cohort of children who were repeatedly referred but did not require treatment points to the challenge of over-referral when based on photoscreening refractive error alone. These findings illustrate some of the potential limitations of the screening program and could be relevant information for both Parents and FMP / Pediatricians.

Guimarães *et al*[15] published a cost-effectiveness analysis based on a prospective school-based screening (coverage for 91% of all children) at 3-4 years of age, and used lower-threshold photoscreening criteria than those applied in the RSVI screening program. They concluded that photoscreening alone achieved a 97% sensitivity and 83% specificity for amblyopia, with 19% of the whole population being referred. Adding UCVA to the PLX achieved a 96% sensitivity, 93% specificity, and would reduce referrals to 9% of the whole population. In our sample, the higher-threshold RSVI criteria alone, without UCVA, and applied to 2 and 4-year-old children, led to a referral rate of 11.1%. Based on our sample, adding UCVA to the 2-year-old screening would be ineffective (74.3% did not cooperate), but could be relevant at 4 years of age, as 84.6% cooperated for VA measurement. Based on the data from Guimarães *et al*, it seems likely that a lower-threshold referral criteria paired with UCVA, at 4 years-of-age, would result in a similar or even lower referral rate compared to what we are receiving now (9% *vs* 11.1%), but with the bonus of increased sensitivity for other outcomes that require ophthalmological observation, besides amblyopia. Although our sample is not representative of the general population, and likely contains a group with a higher prevalence of disease and more edge cases (disease *versus* no-disease), UCVA improved the AUC of all our models for amblyopia, refractive errors that needed spectacle correction, strabismus and a combination

of all of the above, albeit with a more modest improvement in the strabismus models (where stereopsis measurement was superior) than in the others.

In another related publication,[16] Guimarães *et al* discuss how the low rate of strabismus in their study might have been related to the lower adhesion rate of children already being treated for strabismus at the time of the screening. The same might be happening to the RSVI, as already diagnosed patients might be skipping the RSVI screening program, and this would help explain the low prevalence of strabismus in the SRG (1.8%). However, in our sample, 18/45 (40%) of the strabismus cases observed had a negative RSVI screening exam, and the RSVI photoscreening referral criteria alone performed poorly for strabismus detection (AUC 0.511). Adding stereopsis improved these models (AUC 0.862), but still had a low 69.1% sensitivity, as expected by the exam's limitations and varying strabismus characteristics. Although this cannot be generalized to the performance of the RSVI in the general population, it supports the hypothesis that a photoscreening-only program is likely missing a relevant number of strabismus cases that, even if not associated with amblyopia, need an ophthalmology referral.

Taking these results into account, the authors suggest that a multi-modal and/or tiered, age-adapted, screening approach might be advantageous over the current single-modality, single referral criteria screening at both 2 and 4 years of age. A protocol with higher-thresholds photoscreening in pre-verbal children, followed by lower-thresholds photoscreening + UCVA testing in 3-4 years-old children would enhance sensitivity beyond refractive risk alone, while controlling referral volume. Adding stereoacuity testing to the screening remains of uncertain usefulness; it was significantly more associated with strabismus than the other variables available in our dataset, but the very high prevalence of strabismus in our population compared to the expected prevalence in the general population is most likely overvaluing its impact. Additionally, despite being an improvement, it had a sensitivity for strabismus lower than 70%, which is still inadequate for a screening tool.

This study has significant limitations. Its observational, cross-sectional, and single-center hospital design limits the generalizability of the findings to other similar hospital populations, and cannot be directly used to estimate the effectiveness of the screening program. We had 10.3% and 14.0% no-shows in the SRG and STG groups, which might contain an important selection bias. A significant portion of the cohort had an indeterminate amblyopia status, a common challenge in this age group that reduced the statistical power for the regression analysis. A sensitivity analysis showed that a very high number of amblyopia cases in the indeterminate group would greatly influence these results. Therefore, it's important to note that these results represent only those cases that cooperate for visual acuity measurements, and do not include children with presumed amblyopia.

To our knowledge, there are still no published population-based prospective studies that review both positive and negative screening patients and are able to more adequately measure the RSVI program's diagnostic performance for amblyopia and other ophthalmologically relevant outcomes. A future multi-centric prospective study that also includes different screening protocols and a cost-effectiveness analysis would further support evidence-based changes to the RSVI Program.

CONCLUSION

A primary care-based photoscreening program and traditional clinical referrals are highly complementary pathways for identifying children at risk of vision loss. The screening program is effective at detecting younger children with asymptomatic amblyogenic refractive errors, while clinical suspicion remains vital for identifying strabismus. The diagnostic accuracy for amblyopia and its risk factors might be improved with age-adapted, multimodal screening strategies that combine photoscreening with functional tests like uncorrected visual acuity. Future studies into the cost-effectiveness of these adaptations might provide further insights to guide an evidence-based improvement to the current RSVI model.

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ANNEX 1. The Complementary Roles of Photoscreening and Clinical Referrals for Amblyopia Risk Factor Detection.

Table 1. Sensitivity Analysis for Glasses Prescription.

Outcome	SRG (n=338)	STG (n=203)	*p*-value*
Glasses Prescribed (Clinician Discretion)	115 (34.0%)	64 (31.5%)	0.550
Need for Glasses (AAPOS 2021 Criteria)	105 (31.1%)	36 (17.7%)	**<0.001**

* Pearson's Chi-square test.

Applying standardized AAPOS thresholds reveals that a significant number of prescriptions on STG were not due to potentially amblyogenic refractive errors, but likely due to other factors. To compare two different outcomes (glasses prescribed versus need for glasses) within a single group, the McNemar's Test was also performed. This confirmed that the difference between these two outcomes within the SRG was not statistically significant (p=0.661) but within the STG it was (p<0.001).

Table 2. Prevalence of Strabismus and Glasses Prescription by Age and Referral Group.

Age Group	Referral Group	N	Strabismus, n (%)	Glasses prescribed, n (%)
2 years	SRG	144	4 (2.8%)	52 (36.1%)
	STG	58	11 (19.0%)	14 (24.1%)
3 years	SRG	51	1 (2.0%)	16 (31.4%)
	STG	50	7 (14.0%)	15 (30.0%)
4 years	SRG	97	1 (1.0%)	34 (35.1%)
	STG	46	10 (21.7%)	17 (37.0%)
5 years	SRG	46	0 (0.0%)	13 (28.3%)
	SRG	49	11 (22.4%)	18 (36.7%)

When stratified by age, strabismus remains consistently higher in STG, while spectacle prescription skews toward SRG at 2 – 3 years.

Table 3. Sensitivity Analysis for Missing Amblyopia Data.

Scenario	Group	Amblyopia Cases (n)	Denominator (N)	Prevalence (%)	*p*-value (SRG *vs* STG)
Primary Analysis (Complete-Case)	SRG	12	186	6.5%	0.925
	STG	9	134	6.7%	
Best-Case Scenario (Indeterminate = No Amblyopia)	SRG	12	338	3.6%	0.776
	STG	9	203	4.4%	
Worst-Case Scenario (Indeterminate = Amblyopia)	SRG	164	338	48.5%	**0.028**
	STG	78	203	38.4%	

SRG: Screening Referral Group; STG: Standard Referral Group. The primary analysis is recalculated based on complete-case data. *p*-values are from Chi-square tests. Sensitivity bounds indicate conclusions are robust unless an implausibly high share of the indeterminate cohort had amblyopia.